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Doping of Co, Zn, and Cr in iron oxide magnetic nanosystems: impact on protein corona composition

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Introduction: Lung cancer is the second most common cancer in adults, with 32,560 new cases and 28,618 deaths estimated from 2023 to 2025 in Brazil [1]. Magnetic hyperthermia, successfully tested in glioblastoma, is a promising technique that employs magnetic nanoparticles subjected to an alternating magnetic field to increase the temperature of cells, inducing selective death of cancer cells, more sensitive to temperatures close to 42ºC compared to healthy cells [2]. In this context, magnetic nanosystems with a thermal self-regulation system are promising for combined use in the treatment of cancer, due to their unique physicochemical properties. These properties are directly related to synthesis, morphology, and dimensions, which, in turn, influence the cellular internalization pathway [3]. Objective: To evaluate the effect of the interaction of different magnetic nanosystems particles on cytotoxicity, internalization, and intracellular trafficking in lung cancer models (A549). Methods: Magnetic iron oxide nanoparticles (MIONs) were obtained, pure and doped with Co/Zn/Cr, by coprecipitation. The materials were characterized by XRD, TEM, DLS, Zeta Potential, and FTIR before and after culture medium contact. The protein corona was identified by mass spectrometry. The internalization after specific pathway inhibition in A549 cells was analyzed by fluorescence microscopy and cytotoxicity was assessed by MTT. Results: The XRD diffraction peaks were characteristic of the intended magnetite and ferrite. The FTIR analysis showed the presence of the functional group (Fe-O_ 540 cm-1), confirming Fe3O4 in the material composition. Additionally, the protein adsorption was confirmed by the appearance of the band at 1500 cm-1 (amine groups). In TEM micrography, we observed a spherical shape for pure MIONs and a cubic shape for that doped with Co/Zn/Cr, with decreasing size when doped. DLS analysis in water showed a bimodal distribution of hydrodynamic diameter around 150 and 950 nm for both particles. Moreover, after contact with cellular medium, the size of both particles increased of ~100 nm, probably due to protein adsorption. A decreasing Zeta Potential of the nanosystem resuspended in medium culture compared with water was observed, confirming protein adsorption on the material surfaces. These proteins were identified by mass spectrometry, showing 15 proteins adsorptions in common between the two nanosystems, and 161 exclusively adsorbed by doped nanosystems, suggesting different endocytic processes. This will be confirmed by fluorescence analysis after specific pathway inhibition. Cytotoxicity analyses were performed by MTT after cell interaction with 100, 300, and 500 ?g/ml, showing low cytotoxicity of both materials tested.